American Journal of Hematology 61:159–163 (1999)

Advanced Stage and Unfavorable Hodgkin's Disease in the Chinese—a 20-Year Experience

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We retrospectively analyzed 57 patients with advanced stage (stage III/IV) or unfavorable (presence of B symptoms or bulky disease) Hodgkin's disease from January 1977 to December 1997. There were 29 male and 28 female patients. The median age was 27 years old (range, 13–59). Lactate dehydrogenase levels ranged from 104 units/l to 2320 units/l (median, 433). Eighteen (31.6%), 13 (22.8%), and 26 (45.6%) patients had stage II bulky, stage III, and stage IV disease, respectively. Twenty-five (44%) patients had B symptoms. One (1.8%), 3 (5.3%), 36 (63.2%), and 17 (29.8%) had lymphocyte predominant, lymphocyte depleted, nodular sclerosis, and mixed cellularity histology, respectively. Chemotherapy regimens included mechlorethamine, vincristine, procarbazine, prednisone (MOPP) (n = 9), adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) (n = 23), MOPP alternating with ABVD (*n* = 13), and COPP-ABV hybrid (n = 12). Complete remission was achieved in 47 (82.4%) patients. Eleven patients (23%) relapsed after the first complete remission and four (36%) attained a second complete remission with salvage chemotherapy. Projected overall survival was 69.0% at 10 years and 20 years. Disease-free survival rates were 71% at 10 years and 20 years. Of the potential prognostic factors analyzed (age, sex, stage, lactate dehydrogenase, serum albumin level, regimen, B symptoms and bulky disease) by using the Cox regression model, only a low albumin level was found to adversely affect overall survival (*P* = 0.003). In conclusion, despite the relative low incidence of Hodgkin's disease in Hong Kong Chinese, the treatment outcomes in patients with advanced stage or unfavorable Hodgkin's disease is comparable to Caucasian patients. Am. J. Hematol. 61:159–163, 1999. © 1999 Wiley-Liss, Inc.

Key words: Hodgkin's disease; China; chemotherapy

INTRODUCTION

Although radiation therapy is curative for localized Hodgkin's disease (HD), the treatment of choice for advanced stage HD is combination chemotherapy [1,2]. Since the early 1970s, mechlorethamine, vincristine, procarbazine, prednisone (MOPP) was shown to be an effective combination with a significant remission rate and disease-free survival [3,4]. Subsequent attempt to manage patients resistant to or relapsing from MOPP led to the development of the non-cross-resistant adriamycin, bleomycin, vinblastine, dacarbazine (ABVD). Clinical studies confirmed the efficacy of ABVD and that important long-term side effects associated with the alkylator-based MOPP regimen such as infertility and secondary leukemia are much less frequent [6]. As a result, combination of MOPP and ABVD either as the alternating MOPP/ABVD [6,7] or MOPP-ABV hybrid [8] were developed in order to increase the remission and survival rates further.

Whereas HD constitutes 40–45% of all the lymphoma cases in the West, it only accounts for 9.2% in Hong Kong [9–11]. The cause of the low incidence of HD in Hong Kong is not known. In the literature, chemotherapy treatment outcome in advanced stage HD in Chinese is lacking. Moreover, there is an impression that Asian patients with HD does not fare as well as Caucasian patients [11]. This prompted us to analyze Chinese patients with advanced stage or unfavorable HD in Hong Kong.

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Received for publication 29 August 1998; Accepted 6 January 1999

TABLE I. Chemotherapy Regimens

Drug combination	Dose mg/m[1]	Route	Days given[2]
MOPP			
Mechlorethamine (nitrogen mustard)	6	IV	1,8
Vincristine	1.4	IV	1,8
Procarbazine	100	PO	1–14
Prednisone	40	PO	1–14
ChlVPP			
Chlorambucil	6	PO	1–14
Vinblastine	6	IV	1,8
Procarbazine	100	PO	1–14
Prednisone	40	PO	1–14
ABVD			
Doxorubicin	25	IV	1,15
Bleomycin	10	IV	1,15
Vinblastine	6	IV	1,15
Dacarbazine	375	IV	1,15
MOPP/ABVD			
Alternating months of MOPP and ABVD			
MOPP/ABV hybrid			
Mechlorethamine	6	IV	1
Vincristine	1,4 (max 2)	IV	1
Procarbazine	100	PO	1–7
Prednisone	40	PO	1–14
Doxorubicin	35	IV	8
Bleomycin	10	IV	8
Vinblastine	6	IV	8
CEP			
CCNU	80	PO	1
Etoposide (VP-16)	100	PO	1–5
Prednimustine	60	PO	1–5

[1]Denotes milligrams per square meter of body-surface area.
[2]Drug Combinations were given over a 28-day cycle. Numbers shown refer to days of the cycle.

PATIENTS AND METHODS

From January 1977 to December 1997, 57 (56 newly diagnoses and 1 in first relapse from initial radiotherapy) patients with advanced stage (stage III/IV) or unfavorable (presence of bulky disease or B symptoms) HD were diagnosed and treated at the Queen Mary Hospital. The pathological specimens were reviewed and classified according to the Rye classification [12]. Patients were staged clinically according to the Ann Arbor system [13]. Staging procedures included routine laboratory analysis—chest X-ray, bipedal lymphangiogram, computed tomography (CT)—of the thorax and abdomen, and bilateral bone marrow biopsies. Staging laparotomy were performed only if management decisions would be affected. Gallium scan was performed in selected patients. Bulky disease is defined as a mediastinal mass with a maximal diameter exceeding one third the maximal chest diameter on a standing posteroranterior chest X-ray or any mass greater than 8 cm in diameter.

Chemotherapy regimens used are shown in Table I. Patients received six or CR plus two or a maximum of eight courses of combination chemotherapy. The alternating MOPP-ABVD regimen was modified to 12 courses (6 courses each of MOPP alternating with ABVD). Patients who relapsed more than 12 months from CR received the same chemotherapy regimen for reinduction but patients relapsing within 12 months from CR received non-cross-resistant chemotherapy as salvage treatment (Table I). Adjuvant radiotherapy (36–40 Gy) was given to initial sites of bulky disease after completion of chemotherapy.

Response and Survival Analysis

Response was evaluated after completion of six courses of chemotherapy. Patients had restaging procedures and all initial involved sites were reassessed. CR was defined as the disappearance of all symptoms and signs of disease, with complete resolution of all previously abnormal investigations. PR was defined as a regression of the tumor by more than 50% lasting at least 1 month and no detectable new lesions. No response (NR) was defined as a less than 50% decrease in the tumor mass, or tumor growth during therapy, or transient disease regression lasting less than 1 month. Overall survival (OS) was calculated from the date of diagnosis to date of last follow-up or death. Disease-free survival (DFS) was calculated from the day of CR to the day of death, relapse or last follow-up. Survival curves were plotted by the Kaplan–Meier method and compared by the log-rank test. Patients who underwent bone marrow transplantation were censored at the time of transplantation. Prognostic factors (age, sex, stage, lactate dehydrogenase (LDH), albumin level, histological subtype, B symptoms, bulky disease, chemotherapy regimens) to DFS and OS were analyzed by the Cox Regression model. All *P*-values referred to are two-sided. The number of patients in each treatment regimen was small; hence, survival comparison of the different regimens was not performed.

RESULTS

Clinical characteristics of patients were shown in Table II. Our patients had a young median age of 28 years. Nodular sclerosis (n = 36, 63.2% of patients) and mixed cellularity (n = 17, 30%) histologic subtypes constituted the majority of patients in our study. LDH level ranged from 104 units/l to 2320 units/l (median, 433). Nine, 23, 13, and 12 patients received chemotherapy regimens MOPP, ABVD, MOPP alternating with ABVD and COPP-ABV hybrid respectively. Complete remission was achieved in 47 (82.4%) patients. CR was obtained in 77.8% (n = 7), 86.9% (n = 20), 78% (n = 10), and 83% (n = 10) patients receiving MOPP, ABVD, alternating MOPP/ABVD and MOPP-ABVD hybrid regimens, respectively ($P = 0.86$). Of the 10 non-

TABLE II. Initial Patient Characteristics

n	57 (100%)
Sex	
Male	29 (50.9%)
Female	28 (49.1%)
Age	
<40	49 (86%)
>40	7 (14%)
Histologic type	
LP	1 (1.8%)
NS	36 (63.2%)
MC	17 (29.8%)
LD	3 (5.3%)
B symptoms	
Yes	25 (44%)
No	32 (56%)
Bulky disease	
Yes	19 (33.3%)
No	38 (66.7%)
Stage	
II	18 (31.6%)
III	13 (22.8%)
IV	26 (45.6%)
Albumin level	
Normal	30 (52.6)
Below normal	27 (47.4%)
LDH level	
Normal	31 (52.6%)
Above normal	26 (45.6%)
Initial Treatment	
MOPP	9 (15.8%)
ABVD	23 (40.4%)
Alternating MOPP-ABVD	13 (22.8%)
MOPP-ABV hybrid	12 (21.0%)
Radiotherapy	
yes	22 (38.6%)
no	35 (61.4%)

remitters, 3 (30%) were primary chemo-resistant disease and died of progressive disease shortly (5–12 months) after diagnosis. Six non-remitters (60%) attained PR after initial combination chemotherapy. Of these, one defaulted follow-up and two refused further treatment and are currently alive with disease. Three PR patients received radiotherapy to sites of residual disease. Of these three, two had resistant mediastinal disease and died shortly, while one had resolution of the residual disease with radiotherapy but died shortly of progressive disease outside the field of radiotherapy. Eleven of the 47 complete remitters (23.4%) relapsed after initial chemotherapy at a median of 12 months from first remission (range, 2–47 months). Five patients relapsed at sites of initial disease (cervical, three; mediastinal, one; inguinal, one). Of these 11 relapses, four (36.3%) attained second CR with further chemotherapy and three are currently disease-free at 21–54 months from first relapse. Four patients had resistant relapses and died of progressive disease. Three relapsed patients attained a partial response and are still alive with disease.

Projected OS were 69% at 10 years and 20 years (Fig. 1). Projected disease-free survival were 71% at 10 years and 20 years (Fig. 2). Of the potential prognostic factors analyzed (age, sex, stage, LDH, serum albumin level, regimen, B symptoms and bulky disease) by the Cox regression model, only a low albumin level was found to adversely affect OS ($P = 0.003$)(Fig. 3).

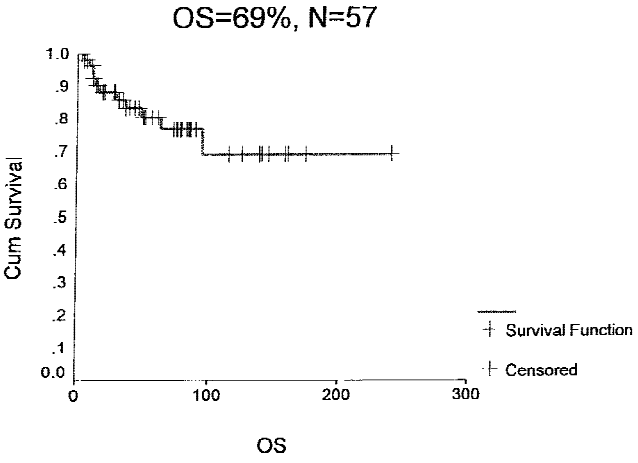

Fig. 1. Projected overall survival.

One patient developed acute myeloid leukemia (AML) 6 years after MOPP therapy and had undergone allogeneic bone marrow transplantation. Another patient developed non-Hodgkin's lymphoma 12 years after MOPP therapy. None of the patients developed secondary solid tumor. There were 11 deaths because of progressive disease. Besides the patient with secondary AML, four other patients underwent bone marrow transplantation, one patient with bone marrow involvement received an allograft at PR, and three received autograft at the second CR.

DISCUSSION

Although HD constitutes 40–45% of all the lymphoma cases in the West, it only accounts for 9.2% in Hong Kong [9–11]. A recent review of the incidence of HD in Asia also shows a much lower incidence rate of around 0.5/100,000 people in China, Japan, Philippines, and Thailand in contrast to 3/100,000 people in the West [11]. The cause of the low incidence of HD in Asia and Hong Kong is not known but has been postulated to be due to genetic and viral factors.

Since the introduction of MOPP regimen in 1964, various clinical trials have confirmed its efficacy [4,14,15]. An update of treatment result showed that MOPP resulted in a CR rate of 84% and a DFS of 54% at 20-year follow-up [4]. ABVD, a non-cross-resistant regimen designed in 1973 to salvage MOPP-resistant patients, resulted in a similar CR rate of 81–83% and a DFS of 64–65% [5,14]. Subsequently, MOPP alternating with

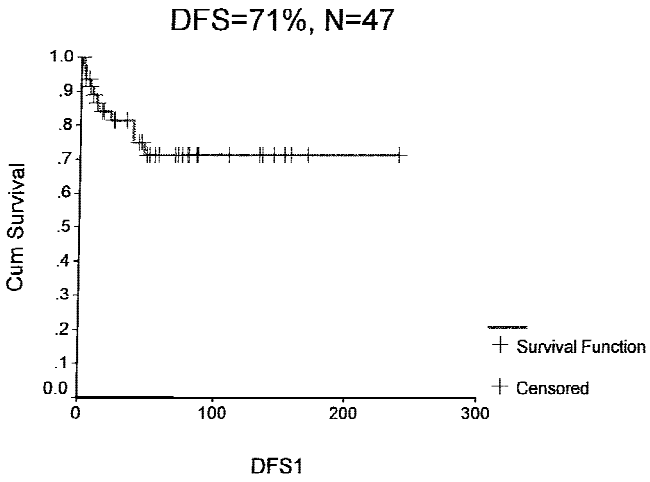

Fig. 2. Projected disease-free survival.

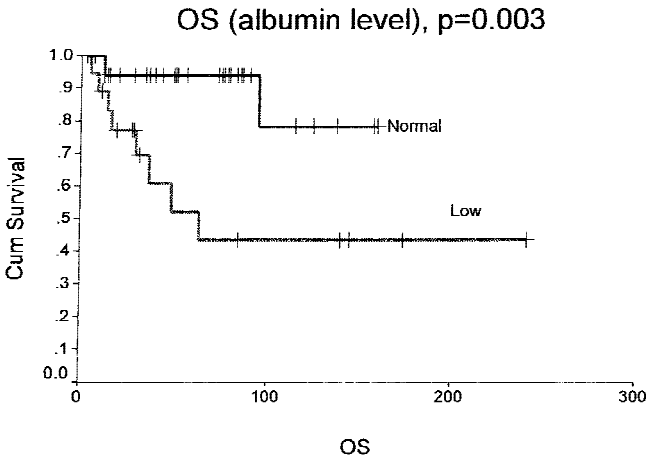

Fig. 3. Albumin level adversely affected overall survival.

ABVD was shown to result in a CR rate of 89% and DFS of 76% at 7 years [6,7]. MOPP-ABV hybrid, designed to test the Goldie–Coleman hypothesis [16], was shown to result in a CR rate of 97% and a DFS of 77% at 7 years [6,17]. Moreover, prospective randomized studies confirmed a superior efficacy of ABVD or ABVD-containing regimens to MOPP [14,15].

Thus, with the use of combination chemotherapy, CR can be attained in 70–90% of Caucasian patients. About one third of the remissions will be followed by a relapse and, thus, the primary treatment regimen will result in the cure of 50–65% of all patients with advanced stage HD. Appropriate salvage chemotherapy for patients with a relapse will rescue a further 10–15% of patients. Thus, current chemotherapy treatment will cure 65–75% of all patients with advanced stage HD [2].

In our study, CR was obtained in 82% of patients and 23% of the complete remitters (n = 11) relapsed. Four (36%) of the relapsed patients attained second CR and three are currently disease-free at 21–54 months from first relapse. Thus, the remission, relapse, and second CR rates are comparable to those found in studies conducted in the West. Moreover, our patients had a projected OS and DFS of 69% and 71% at 10 and 20 years, respectively, which is similar to results in Caucasian patients. Hence, although the small numbers of patients in our study prohibited proper comparison of treatment results with the various chemotherapy regimens, overall, our patients had CR and survival (DFS and OS) rates similar to those of Caucasian patients. Many studies have shown that improvement in failure-free survival or DFS with newer chemotherapy regimens is not translated into improvement in the overall survival [14,15,18]. This is attributed to effectiveness of salvage chemotherapy. Indeed, of the 11 patients who relapsed from initial remission in our study, 36% (n = 4) attained second complete remission with salvage chemotherapy and of three are still disease-free at 21–54 months from first relapse. This is consistent with the high efficacy of salvage chemotherapy in HD.

Studies have shown that advanced age, bulky disease, B symptoms, male sex, lymphocyte-depleted histology and low albumin level at presentation are poor prognostic factors [1,19]. In our cohort, these factors did not turn out to be significant prognostic factors except albumin level ($P = 0.003$). This is due to the small numbers of patients and the selected population of unfavorable disease (advanced stage and unfavorable features) in our study. Moreover, the low albumin level at presentation suggested poor nutritional status in these patients and thus poor tolerability to chemotherapy treatment.

In our study, only one patient developed AML after combination chemotherapy. Similarly, in the update of MOPP treatment results after 20 years, only 1 out of 188 patients developed AML after MOPP alone. On the other hand, other study showed an increased relative risk in the development of secondary AML [20] especially in those receiving combined modality therapy [21] in HD. In contrast, patients who received ABVD had a much lower risk of secondary AML than MOPP [1,6].

Our patients did not show a male preponderance (M: F = 1.04) as compared with studies conducted in the West (M: $F = 1.94$–2.13) [14,15] but this might be due to the small number of patients in our series. B symptoms were less common (44%) in our patients probably because of the inclusion of patients with stage II disease. However, we shared similar features in that nodular sclerosis and mixed cellularity made up the majority (93%) of histology subtypes in our series as compared with 94%–95% in western studies [14,15]. Moreover, we had a relatively young patient population (86% < 40 years old), similar to other studies [14,15].

In conclusion, despite the relative low incidence of HD in Hong Kong Chinese, the treatment outcomes (CR rate and survivals) are comparable to Caucasian patients.

ACKNOWLEDGMENTS

We sincerely thank Professors David Todd and T.K. Chan for their advice in the management of patients. We also thank Dr. Damon Choy and his colleagues for offering radiotherapy for our patients.

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